REMARKS

Claims 1, 4-10 and 14 are pending. A copy of the pending claims is attached for the Examiner's convenience. Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested for the reasons that follow.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 4-10 and 14 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner objects to the limitation "each in an amount sufficient to modulate said cellular proliferative disease". Applicant asserts that the specification provides sufficient guidance for one of skill in the art to know what amount would bring about sufficient modulation of the proliferative disease.

The definiteness of claim language must be determined in light of the teachings in the specification and the prior art. *In re Moore,* 439 F.2d 1232 (CCPA 1971). The present specification provides the teaching necessary for one of skill in the art to understand the meaning of "each in an amount sufficient to modulate said cellular proliferative disease". For example, the specification on page 5, line 19, through page 6, line 11, discloses specific ranges of dosage amounts to be used in practicing the invention. On page 6, lines 2-6, the specification teaches preferred dosage amounts of the hexitols of the invention. On page 6, lines 7-11, the specification teaches preferred dosage amounts of the antiproliferative compound cisplatin.

Additionally, the Example on pages 6-8 sets forth experimental conditions used to obtain modulation of a proliferative cell disease including the dosage of dianhydrogalactitol and cisplatin used to obtain modulation.

Importantly, the specification on page 3, line 22, through page 4, line 12, provides examples of "modulation of a cellular proliferative disease". Techniques to monitor these types of modulations are well known in the art. Additionally, the specification in Example 1, pages 6-8, provides specific methods of determining when a cellular proliferative disease has been modulated.

The teachings of the specification and the general knowledge of one of skill in the art renders the term "each in an amount sufficient to modulate said cellular proliferative disease" definite. Applicant asserts that claims 1, 4-10 and 14 are in compliance with 35 U.S.C. § 112, second paragraph and respectfully requests that the rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1, 4-10 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francis (U.S. Pat. No. 4,797,388, "Francis") further in view of Levin et al. (Cancer Chemother. Pharmacol. 8:125-31 (1982), "Levin"). Applicant respectfully traverses.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must demonstrate a suggestion or motivation in the prior art to modify or combine the teachings of the references to arrive at the claimed invention. Further, the prior art must provide one of ordinary skill with a reasonable expectation of success. Finally, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. M.P.E.P. § 2143.

Applicant respectfully submits that the combination of the cited references, Francis and Levin, would not have provided one of skill in the art with a reasonable expectation of success in practicing the present invention. Levin teaches that a combination of the compounds dianhydrogalactitol and BCNU is more successful in treating brain neoplasm than either compound alone. Francis teaches that the addition of galactitol to a composition that contains a therapeutic agent results in an increase in the stability and solubility of the therapeutic agent.

Cisplatin is mentioned as a possible agent that may be stabilized/solubilized by the addition of galactitol.

The claims of the present invention are directed to methods of treatment of a host with a cellular proliferative disease. The methods comprise contacting the host with a composition consisting essentially of a pharmaceutically acceptable dianhydrogalactitol or analog thereof and a pharmaceutically acceptable antiproliferative agent. The dianhydrogalactitol or analog thereof and antiproliferative agent each are provided in an amount sufficient to modulate the cellular proliferative disease. The antiproliferative agent is selected from the group consisting of antimetabolites, structural protein agents, agents that affect protein synthesis, antibiotics, hormone antagonists, intercalating agents, topoisomerase inhibitors and metal coordination complexes. The claims are not directed to the use of the alkylating agent BCNU for the treatment of a cellular proliferative disease. Further, there is no teaching or motivation provided by these references to substitute the alkylating agent of Levin with an antiproliferative agent selected from the group of antimetabolites, structural protein agents, agents that affect protein synthesis, antibiotics, hormone antagonists, intercalating agents, topoisomerase inhibitors and metal coordination complexes, each of which are not alkylating agents.

Moreover, one of skill in the art would not have a reasonable expectation that the addition of dianhydrogalactitol with one of the claimed antiproliferative compounds would result in a more successful anti-tumor treatment than either compound alone. Francis' disclosure regarding use of galactitol as a carrier for certain therapeutic agents would not provide any expectation of success that the combination of dianhydrogalactitol with an antiproliferative agent selected from the group consisting of antimetabolites, structural protein agents, agents that affect protein synthesis, antibiotics, hormone antagonists, intercalating agents, topoisomerase inhibitors and metal coordination complexes, would result in a treatment more effective than that using dianhydrogalactitol or the anti-proliferative agent alone. It certainly would not have given one of skill in the art the expectation of achieving a chemopotentiator effect described in the present invention.

Furthermore, there is no motivation to combine the cited references. One of skill in the art looking to find additional agents to combine with dianhydrogalactitol to create a new anti-proliferative drug would not look to Francis as a source of potential compounds. Francis is more relevant to the final formulation of a therapeutic drug rather than a source of compounds to use in the early research stage of generating new anti-proliferative drugs. Francis' reference to increased compound stability is to the stability of compound prior to administration to a patient. The stability of therapeutic agents in the presence of galactitol is analyzed by incubating the agent/galactitol composition at 37^0C for one week. The ability of the composition to act as an anti-tumor agent is never addressed. One of skill in the art would have no reason to take the teachings of Francis and combine it with the compounds in Levin to create the present invention. Levin addresses pharmacological benefits of various compounds; Francis addresses formulation of a therapeutic compound to increase its shelf-life.

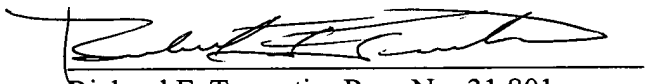
CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance and an early notification of such is solicited. If, upon review, the Examiner feels there are additional outstanding issues, the Applicants respectfully request that the Examiner call the undersigned attorney.

Respectfully submitted,

DORSEY & WHITNEY LLP

Date: 5/12/03



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PENDING CLAIMS

1. (Twice Amended) A method of treatment of a host with a cellular proliferative disease, comprising contacting said host with a composition consisting essentially of a pharmaceutically acceptable dianhydrogalactitol or analog thereof, and a pharmaceutically acceptable antiproliferative agent, each in an amount sufficient to modulate said cellular proliferative disease, wherein said antiproliferative agent is selected from the group consisting of antimetabolites, structural protein agents, agents that affect protein synthesis, antibiotics, hormone antagonists, intercalating agents, topoisomerase inhibitors and metal coordination complexes.

4. (Twice Amended) The method according to claim 1 wherein said antiproliferative agent is an intercalating agent.

5. (Twice Amended) The method according to claim 1 wherein said antiproliferative agent is a metal coordination complex.

6. (Twice Amended) The method according to claim 1 wherein said antiproliferative agent is cisplatin.

7. (Amended) A method according to claim 1 wherein said dianhydrogalactitol or analog thereof is administered before the administration of said antiproliferative agent.

8. (Amended) A method according to claim 1 when said dianhydrogalactitol or analog thereof is administered during the administration of said antiproliferative agent.

9. (Amended) A method according to claim 1 wherein said dianhydrogalactitol or analog thereof is administered after the administration of said antiproliferative agent.

10. The method of claim 1 wherein the modulation of said disease with said composition is greater than that for said antiproliferative agent alone.

14. A method according to claim 1 wherein said cellular proliferative disease is a solid tumor.